

## Smallpox

- First described in Chinese text in 4<sup>th</sup> century AD
- Vaccine developed in late 18<sup>th</sup> century
- Last case in U.S. in 1949
- Last indigenous case on earth in 1977

## Variola Virus

- Orthopoxvirus
- Infects only humans in nature
- May remain viable in crusts for years at room temperature
- Rapidly inactivated by UV light, chemical disinfectants

Smallpox is an acute infectious disease caused by the variola virus. Smallpox is believed to have emerged in human populations about 10,000 BC. A description of smallpox first appeared in a Chinese text in the 4th century. The name variola was first used during the 6th century and is a derivative of the Latin *varius*, meaning spotted or *varus*, meaning pimple. The first efforts to prevent smallpox occurred in China and India in the 8th century, and involved intentional inoculation of a susceptible person with pustular or scab material from a person with smallpox. The term smallpox was first used in Europe in the 15th century to distinguish variola from the great pox (syphilis). In 1796 Edward Jenner demonstrated that smallpox could be prevented by inoculation of a person with material from a cowpox lesion, which led to the first smallpox vaccine. The last case of smallpox in the United States was reported in Texas in 1949. In 1966 the World Health Organization initiated an intensified global smallpox eradication program. The last indigenous case of smallpox on earth occurred in Somalia in October 1977. The World Health Assembly officially certified the global eradication of smallpox in May 1980.

## VARIOLA AND OTHER ORTHOPOXVIRUSES

Smallpox is caused by variola virus. Variola virus belongs to the genus Orthopoxvirus, family Poxviridae. Poxviruses are large brick-shaped viruses with a double stranded DNA genome. They are different from most other DNA viruses in that they replicate in the cytoplasm of the cell rather than in the nucleus. To do this, they produce a variety of proteins not produced by other DNA viruses (e.g., herpes virus). Four orthopoxviruses are known to infect humans: variola, vaccinia, cowpox, and monkeypox. Variola virus infects only humans in nature, although primates and other animals can be infected under laboratory conditions. Vaccinia, cowpox, and monkeypox viruses can infect both humans and other animals in nature.

Variola virus can remain viable for several days in a controlled environment. In temperate climates, crusts from the skin lesions from smallpox patients, in which the virus is contained in a fibrin matrix, can retain viable virus for several years when held at room temperature. The virus survives longer at low temperature and humidity than at higher temperature or humidity. All poxviruses are rapidly inactivated by exposure to ultraviolet light, and chemical disinfectants such as bleach or Lysol®.

Some persons infected with variola major virus have particularly severe illnesses. This suggests that there could be differences in the virulence of strains of the virus. However, no laboratory test has been devised that correlates with virulence in humans. Physiologic factors in the host are probably the more important determinant of severity of the illness.

Smallpox vaccine contains vaccinia virus, not variola virus. Vaccinia is rarely isolated from animals outside the laboratory. There are multiple strains of vaccinia virus that have different lev-

els of virulence for humans and animals. Vaccinia virus can also be genetically engineered to accept DNA and express other antigens, and has been used as a vector in laboratory experiments. Cowpox virus was probably the virus that Edward Jenner originally used as a vaccine for smallpox. The virus has many natural hosts, including cows, rodents, cats, elephants, and is found in nature primarily in Europe. Monkeypox infects primates, anteaters and squirrels, and is found in western and central Africa.

## **PATHOGENESIS**

Variola virus infection is initiated when the virus comes into contact with the oropharyngeal or respiratory mucosa. Virus multiplication then occurs in regional lymph nodes. An asymptomatic viremia develops 3 or 4 days after infection which is followed by virus replication, probably in the bone marrow, spleen, and lymphatics. A second viremia begins about 8-10 days after infection and is followed by the first symptoms of illness (prodromal stage), fever and toxemia. The virus localizes in small blood vessels of the dermis and in the oral and pharyngeal mucosa. In the skin this results in the characteristic maculopapular rash, which evolves into vesicles, then pustules.

## **CLINICAL FEATURES**

Two clinical forms smallpox have been described. While both forms are caused by variola virus, they are caused by different strains of the virus distinguishable by specific biologic properties (such as growth characteristics in cell culture and DNA structure).

**Variola major** is the severe form of smallpox, with a more extensive rash, higher fever, and a greater degree of prostration. Variola major has a case fatality rate of 30% or more. The last case of variola major occurred in Bangladesh in 1975. Variola minor was first described in South Africa in 1904, and in the United States in 1913. Variola minor is a much less severe disease, with a case fatality rate of 1% or less. **Variola minor** was endemic in some countries of Europe and of North and South America, and in many parts of Africa. The last case of variola minor occurred in Somalia in October 1977, and was the last case of indigenous smallpox on earth.

There are **four principal clinical presentations of variola major**, based on the Rao classification (1972). The relative vigor of the immune response to the infection probably determined the clinical presentation of the infection. The classification is based on the nature and evolution of the lesions: ordinary (most frequent); modified (mild and occurring in previously vaccinated persons); flat; and hemorrhagic. Flat and hemorrhagic smallpox are severe, uncommon forms and are usually fatal. In addition, variola sine eruptione (smallpox without rash) is a febrile illness occurring after the usual incubation period. It is seen generally in vaccinated persons and can be confirmed only by antibody studies or, rarely, by virus isolation. Subclinical (asymptomatic) infections with variola virus also occurred, but is not common and generally occurs in

### **Smallpox Pathogenesis**

- Virus contact with oropharyngeal or respiratory mucosa
- Virus replication in regional lymph nodes
- Viremia on about 8<sup>th</sup> day of infection
- Virus replication in oral and pharyngeal mucosa and skin

### **Smallpox Clinical Presentations**

- Variola major
  - Severe illness
  - Case fatality rate of  $\geq 30\%$
- Variola minor
  - Less severe
  - Case fatality of  $\leq 1\%$

### **Clinical Presentations of Variola Major**

- Ordinary ( $\geq 90\%$  of cases in unvaccinated people)
- Modified (mild; occurs in previously vaccinated people)
- Flat (uncommon; usually fatal)
- Hemorrhagic (uncommon; usually fatal)

## Smallpox Prodrome

- Incubation period 12 days (range 7-19 days)
- Prodrome
  - abrupt onset of fever  $\geq 101^{\circ}\text{F}$
  - malaise, headache, muscle pain, nausea, vomiting, backache
  - lasts 1-4 days
  - not infectious until lesions develop in mouth

## Smallpox Rash

- Enanthem (mucous membrane lesions) appears approx. 24 hours before skin rash
- Minute red spots on the tongue and oral/pharyngeal mucosa
- Lesions enlarge and ulcerate quickly
- Virus titers in saliva highest during first week of exanthem

## Smallpox Rash

- Exanthem (skin rash) appears 2-4 days after onset of fever
- First appears as macules, usually on the face
- Lesions appear on proximal extremities, spread to distal extremities and trunk

## Smallpox Rash Evolution

Stage	Days after Rash Onset
Macules	0-1
Papules	2-3
Vesicles	3-5
Pustules	6-12
Crusts	13-20
All crusts separated	21-28

vaccinated people.

The **incubation period** of smallpox averages 12 days, with a range of 7 to 19 days. During this period the patient is well. The **prodrome** or pre-eruptive stage of the illness then starts abruptly, with fever (usually  $102\text{--}104^{\circ}\text{F}$ ), malaise, headache, muscle pain, prostration, and often nausea and vomiting and backache. The person usually appears quite ill. The prodrome usually lasts 1-4 days. The person is not infectious until the end of the prodrome, when lesions develop in the mouth.

## ORDINARY SMALLPOX

Ninety percent or more of smallpox cases among unvaccinated persons are of the ordinary type. The prodromal stage is of varying severity. By the third or fourth day of illness the temperature usually falls and the patient feels somewhat better. At this point the rash appears. The rash appears first as an enanthem - minute red spots on the tongue and oral and pharyngeal mucosa, about 24 hours before the appearance of rash on the skin. Lesions in the mouth and pharynx enlarge and ulcerated quickly, releasing large amounts of virus into the saliva about the time the cutaneous rash first becomes visible. Virus titers in saliva are highest during the first week of illness, corresponding with the period during which patients are most infectious.

The exanthem (skin rash) usually appears 2-4 days after the onset of fever as a few macules (known as "herald spots") on the face, particularly on the forehead. Lesions then appear on the proximal portions of the extremities, then spread to the distal extremities and the trunk. Usually the rash appears on all parts of the body within 24 hours.

By the second day of the rash, the macules become raised papules. By the third or fourth day the lesions become vesicular, containing first an opalescent fluid, which then becomes opaque and turbid within 24-48 hours. The skin lesions of smallpox typically are surrounded by a faint erythematous halo. The distended vesicles often have a central depression or dimple of varying size, referred to as "**umbilication**." Umbilication often persists into the pustular stage, but as the lesion progresses it usually becomes flattened because of adsorption of fluid. Umbilication is less common in other vesicular or pustular rash illnesses, particularly in varicella.

By the sixth or seventh day, all the skin lesions are pustules. Between 7 and 10 days the pustules mature and reach their maximum size. The pustules are sharply raised, typically round, tense, and firm to the touch. **The pustules are deeply embedded in the dermis, giving them the feel of a small bead in the skin.** The skin lesions are often described as "shotty". Fluid is slowly absorbed from the pustules and by the end of the second week the pustules begin to form a crust. During the third week the crusts separate, leaving depigmented skin which eventually become pitted scars. Fever usually rises again by the seventh or eighth day of the

illness and continues to remain high throughout the vesicular and pustular stages, until crusts have formed over all the lesions.

The rash usually develops as a single crop. Consequently, **lesions in a particular part of the body are at about the same stage of development**, although they may be different sizes. The distribution of the rash is centrifugal: most dense on the face; more dense on the extremities than on the trunk; and on the extremities, more dense on the distal parts than on the proximal. The palms of the hands and soles of the feet are involved in the majority of cases.

In general, the severity of the clinical picture parallels the extent of the rash. In some cases, the pustular skin lesions on the extensor surfaces of the extremities and face are so numerous they became confluent. Patients with confluent smallpox often remain febrile and toxic even after scabs have formed over all the lesions. In one case series the case-fatality rate in confluent smallpox was 62%.

### **MODIFIED SMALLPOX**

Modified smallpox relates to the character of the eruption and the rapidity of its development. This form of smallpox occurs mostly in previously vaccinated patients. The prodromal illness occurs but may be less severe than in ordinary type smallpox. Fever during evolution of the rash is usually absent. The skin lesions tend to evolve more quickly, are more superficial, and may not show the uniformity characteristic of more typical smallpox. The lesions are often few in number, but even when they are numerous, or even confluent, they usually evolve rapidly. Modified smallpox is rarely, if ever, fatal. This form of varicella major is more easily confused with chickenpox.

### **FLAT (MALIGNANT) SMALLPOX**

Flat-type smallpox is so called because the lesions remain more or less flush with the skin at the time when raised vesicles form in ordinary-type smallpox. It is not known with certainty why some persons develop this type of disease. In a large series of persons hospitalized with smallpox in India, flat-type smallpox accounted for 5%-10% of cases, and the majority (72%) were in children. The prodrome is severe and lasts 3-4 days. Constitutional symptoms are severe and continue after the appearance of the rash. The fever remains elevated throughout and the patient has severe toxic symptoms. The rash on the tongue and palate is usually extensive. The skin lesions mature very slowly. By the seventh or eighth day the lesions are flat and appear to be buried in the skin. Unlike ordinary type smallpox the vesicles contain very little fluid and do not appear umbilicated. The lesions are soft and velvety to the touch, and may contain hemorrhages. Respiratory complications are common. The prognosis for flat-type smallpox is grave and most cases are fatal.

#### **Smallpox Rash**

- Vesicles often have a central depression ("umbilication")
- Pustules raised, round, firm to the touch, deeply embedded in the skin
- Lesions in any one part of the body are in same stage of development
- Most dense on face and distal extremities (centrifugal distribution)
- Lesions on palms and soles ( $\geq 50\%$  of cases)

#### **Modified Smallpox**

- Occurs in previously vaccinated persons
- Prodrome may be less severe
- No fever during evolution of rash
- Skin lesions evolve more quickly
- Rarely fatal
- More easily confused with chickenpox

#### **Flat Smallpox**

- Severe prodrome
- Fever remains elevated throughout course of illness
- Extensive enanthem
- Skin lesions soft and flat, contain little fluid
- Most cases fatal

## Hemorrhagic Smallpox

- Prolonged severe prodrome
- Fever remains elevated throughout course of illness
- Early or late hemorrhagic signs
- Bleeding into skin, mucous membranes, GI tract
- Usually fatal

## HEMORRHAGIC SMALLPOX

Hemorrhagic smallpox is a severe and uncommon form of smallpox that is accompanied by extensive bleeding into the skin, mucous membranes and gastrointestinal tract. In the large Indian series, hemorrhagic disease occurred in about 2% of hospitalized patients; the majority of cases were among adults, and pregnant women appear to be at increased risk. The prodromal stage, which can be prolonged, is characterized by fever, intense headache and backache, restlessness, a dusky flush or sometimes pallor of the face, extreme prostration, and toxicity. There is little or no remission of fever throughout the illness. Hemorrhagic manifestations can occur early or late in the course of the illness. In the early, or fulminating form hemorrhagic manifestations appear on the second or third day as subconjunctival bleeding, bleeding from the mouth or gums and other mucous membranes, petechiae in the skin, epistaxis, and hematuria. Death often occurs suddenly between the fifth and seventh days of illness, when only a few insignificant maculopapular cutaneous lesions were present. In patients who survive for 8-10 days the hemorrhages appear in the early eruptive period, and the rash is flat and does not progress beyond the vesicular stage.

## VARIOLA SINE ERUPTIONE AND SUBCLINICAL INFECTION

Febrile illness sometimes occurs among vaccinated contacts of cases of smallpox, with the sudden onset of temperature of about 39°C, headache and sometimes backache. The attack often subsides within 48 hours and the temperature returns to normal. Although these symptoms could be caused by other infections, laboratory investigation may show a significant increase in variola antibody following such an attack. There is evidence of true subclinical infection with variola major virus (*i.e.*, serologic evidence of infection with no symptoms), typically in recently vaccinated household contacts of smallpox cases. Persons with subclinical infections have not been shown to transmit the infection to contacts.

## COMPLICATIONS

**Secondary bacterial infection of the skin** is a relatively uncommon complication of smallpox. When this occurred, the fever usually remained elevated. **Arthritis** occurs in up to 2% of cases, most commonly in children. **Respiratory complications** (*e.g.*, bronchitis, pneumonitis, or pneumonia) sometimes develop on about the eighth day of the illness, and can be either viral or bacterial in origin. **Encephalitis** occasionally occurs that is indistinguishable from the acute perivascular demyelination observed as a complication of infection due to vaccinia, measles, and varicella.

In fatal cases, **death** usually occurs between the tenth and sixteenth days of the illness. The cause of death from smallpox is not

## Smallpox Complications

- Bacterial infection of skin lesions
- Arthritis
- Respiratory
- Encephalitis
- Death
  - 30% overall for ordinary smallpox
  - 40%-50% for children <1 year
  - >90% for flat and hemorrhagic smallpox

clear, but the infection is now known to involve multiple organs. Circulating immune complexes, overwhelming viremia, or an uncontrolled immune response may be contributing factors. The overall case fatality rate for ordinary-type smallpox is about 30%. However, the fatality rate for children <1 year of age is 40%-50%. The fatality rate for flat-type and hemorrhagic smallpox is  $\geq 90\%$ . The case fatality rate for variola minor is 1% or less.

**Sequelae** of smallpox includes scarring, which is most common on the face, blindness resulting from corneal ulceration and scarring, and limb deformities due to arthritis and osteomyelitis. There is no evidence of chronic or recurrent infection with variola virus.

## DIFFERENTIAL DIAGNOSIS

The disease that most closely resembles smallpox is varicella (chickenpox). **The most important differentiating feature between smallpox and varicella, as well as other rash illnesses is the presence of a prodrome - fever and other symptoms before rash onset.** A person with smallpox will have a severe, febrile prodrome that begins 1-4 days before the onset of the rash. The fever is high, usually 102° - 104°F but always at least 101°F. People with varicella have a short, mild prodrome, or no prodrome at all before onset of the rash, and have little or no fever before rash onset. **If there is no history of a febrile prodrome, smallpox is not likely.** In addition to fever, the prodrome of smallpox is associated with one or more additional symptoms, such as prostration, headache, backache, chills, abdominal pain or vomiting. Patients are frequently too ill to engage in normal activities. During its prodromal phase, some persons with varicella - particularly adults - may feel tired or have a low grade fever but most don't feel very ill.

**Another important differentiating feature of smallpox and varicella is the appearance, evolution, and distribution of the rash.** Although there may be some overlap in the appearance of the lesions, particularly early after rash onset, classic smallpox looks very different than varicella. Smallpox lesions are deep in the dermis, and feel hard to the touch. They are round and well circumscribed. As they evolve they may become confluent or umbilicated. The varicella rash is superficial, and the lesions appear to be delicate, and not as well circumscribed. Confluence and umbilication are uncommon in varicella. Smallpox rash lesions appear in a single crop and lesions on any part of the body are in the same stage of development. Lesions are more dense on the extremities than on the trunk and often involve the palms and soles (*i.e.*, centrifugal distribution). In contrast, the rash of varicella appears in several crops, so papules, vesicles, and crusts are seen simultaneously on the same part of the body and new lesions continue to appear for several days. Lesions are typically more dense on the trunk than on the extremities.

For the first 2-3 days the smallpox rash is maculopapular. At this stage of the illness smallpox could be confused with other febrile

### Differential Diagnosis

The most important differentiating feature between smallpox and other rash illnesses is the presence of fever before rash onset.

### Differential Diagnosis

- | Smallpox                   | Varicella                |
|----------------------------|--------------------------|
| • Severe, febrile prodrome | • Mild or no prodrome    |
| • 1-4 days before rash     | • Little or no fever     |
| • $\geq 101^\circ\text{F}$ | • No associated symptoms |
| • Other symptoms:          |                          |
| - prostration              |                          |
| - headache                 |                          |
| - backache                 |                          |
| - chills                   |                          |
| - abdominal pain           |                          |
| - vomiting                 |                          |

### Differential Diagnosis

- | Smallpox                               | Varicella                              |
|--|--|
| • Deep, hard lesions                   | • Superficial lesions                  |
| • Round, well circumscribed            | • Not well circumscribed               |
| • Confluent or umbilicated             | • Confluence and umbilication uncommon |
| • Lesions at same stage of development | • Lesions at all stages of development |

## Smallpox Major Criteria

- Febrile prodrome 1-4 days before rash onset; fever of  $\geq 101^\circ\text{F}$ , and at least 1 additional symptom\*
- Rash lesions deep, firm/hard, round and well circumscribed
- On any one part of the body lesions in same stage of development

\*Prostration, headache, backache, chills, vomiting or severe abdominal pain

## Smallpox Minor Criteria

- Greatest concentration of lesions on face and distal extremities
- Lesions first appeared on oral mucosa/palate, face, forearms
- Patient appears toxic or moribund
- Lesions evolve from macules to papules to pustules over days
- Lesions on palms and soles

illnesses with maculopapular rash, such as measles and rubella.

Other common conditions that might be confused with smallpox are summarized in the Table. In addition there are exceedingly rare causes, such as rickettsial pox and monkeypox. A small percentage of smallpox cases present with hemorrhagic smallpox or a flat type rash. Both variants are highly lethal. Hemorrhagic smallpox can be mistaken for meningococcemia.

COMMON CONDITIONS THAT MIGHT BE CONFUSED WITH SMALLPOX

CONDITION	CLINICAL CLUES
Varicella (primary infection with varicella-zoster virus)	Most common in children <10 years; children usually do not have a viral prodrome
Disseminated herpes zoster	Immunocompromised or elderly persons; rash looks like varicella, usually begins in dermatomal distribution
Impetigo ( <i>Streptococcus pyogenes</i> , <i>Staphylococcus aureus</i> )	Honey-colored crusted plaques with bullae are classic but may begin as vesicles; regional not disseminated rash; patients generally not ill
Drug eruptions	Exposure to medications; rash often generalized
Contact dermatitis	Itching; contact with possible allergens; rash often localized in pattern suggesting external contact
Erythema multiforme minor	Target, "bull's eye", or iris lesions; often follows recurrent herpes simplex virus infections; may involve hands & feet (including palms & soles)
Erythema multiforme (incl. Stevens Johnson Syndrome)	Major form involves mucous membranes & conjunctivae; may be target lesions or vesicles
Enteroviral infection esp. Hand, Foot and Mouth disease	Summer & fall; fever & mild pharyngitis 1-2 days before rash onset; lesions initially maculopapular but evolve into whitish-grey tender, flat often oval vesicles; peripheral distribution (hands, feet, mouth, or disseminated)
Disseminated herpes simplex	Lesions indistinguishable from varicella; immunocompromised host
Scabies; insect bites (incl. fleas)	Itching is a major symptom; patient is not febrile & is otherwise well
Molluscum contagiosum	May disseminate in immunosuppressed persons

CDC has developed criteria that can be used to categorize patients into high, moderate or low risk for smallpox using major and minor diagnostic criteria. There are 3 major smallpox criteria:

1. febrile prodrome (fever  $\geq 101^\circ\text{F}$ ) 1-4 days before rash onset and at least one of the following systemic complaints: prostration, headache, backache, chills, vomiting or abdominal pain;
2. rash lesions are deep in the skin, firm or hard to the touch, round and well circumscribed, and may become umbilicated or confluent as they evolve;
3. on any one part of the body all the lesions are in the same stage of development (*i.e.*, all are vesicles or all are pustules).

There are five minor smallpox criteria:

1. the distribution of the rash is centrifugal (*i.e.*, the greatest concentration of lesions is on the face and distal extremities with relative sparing of the trunk);
2. the first lesions of the rash appears on the oral mucosa or palate, or on the face or forearms;
3. the patient appears toxic or moribund;
4. lesions progress slowly (*i.e.*, the individual lesions evolve from macules to papules to pustules; each stage lasts 1-2 days);
5. lesions on the palms or soles.

A person is considered at **high risk** for smallpox if he or she meets all three major criteria. Immediate action should be taken to make sure that contact precautions and respiratory isolation are in place. These patients should be reported to local health authorities immediately. A person considered at **moderate risk** of smallpox must have a febrile prodrome and either one other major criterion or  $\geq 4$  minor. These patients should be isolated and be evaluated urgently to determine the cause of the illness. Persons classified as high or moderate risk be seen in consultation with a specialist in infectious diseases and/or dermatology whenever possible. Any person who did not have a febrile prodrome is considered **low risk**, as are persons who had a febrile prodrome and less than 4 minor criteria. These patients should be managed as clinically indicated.

## LABORATORY DIAGNOSIS

For a patient who meets the criteria for moderate risk, **the most important laboratory procedure is rapid diagnostic testing for varicella zoster virus (VZV)**. Laboratory testing should be done in consultation with an infectious disease or dermatology specialist. There are a variety of rapid methods for detecting VZV in clinical material. The most useful is direct fluorescent antibody, or DFA. This method detects VZV directly in cells using anti-VZV antibody conjugated to fluorescein dye. DFA is very sensitive and specific but is critically dependent on careful collection of material from a lesion. Detection of VZV DNA by polymerase chain reaction testing of vesicular fluid or scabs can also be used for rapid detection of VZV in clinical material. Virus particles consistent with VZV can be detected using electron microscopy. Rapid diagnostic testing for VZV is generally available in at least one facility in all large cities, and in some local and state health department facilities.

Currently, laboratory procedures for variola virus in clinical specimens should be done only by the Centers for Disease Control and Prevention in Atlanta. If the patient's clinical characteristics indicate a high risk for smallpox, or if VZV testing of a vesicular or pox-like rash is negative, the state health department should be contacted immediately. The diagnosis of an orthopoxvirus infection can be made rapidly by electron microscopic examination of pustular fluid or scabs. Differentiation of orthopoxviruses is made by nucleic acid-based testing, such as PCR, and by culture. Serologic tests have also been developed to assist in the diagnosis of acute orthopoxvirus infection.

## MEDICAL MANAGEMENT

**A suspected case of smallpox is a public health and medical emergency.** Any person whose clinical characteristics meet the clinical case definition for smallpox (see below) must be isolated and reported immediately to the local and/or state health department.

### Risk of Smallpox by Clinical History and Examination

- High risk
  - febrile prodrome
  - classic smallpox lesions
  - same stage of development
- Moderate risk
  - febrile prodrome
  - 1 major OR  $\geq 4$  minor criteria
- Low risk
  - no febrile prodrome
  - febrile prodrome and  $< 4$  minor criteria

### Laboratory Confirmation

- Rapid diagnostic testing for varicella zoster virus (DFA, IFA, PCR)
- Electron microscopy (may identify Orthopoxvirus but not specific for variola)
- Culture
- Nucleic acid-based testing
- Serologic testing

Smallpox Medical Management

- Notify public health authorities immediately for suspected case
- Strict respiratory and contact isolation
- Supportive care
- Antiviral agents?

**Strict respiratory and contact isolation of confirmed or suspected smallpox patients is critical to limit the exposure to the virus.** Smallpox patients are infectious until all crusts have separated. Although droplet spread is the major mode of person to person smallpox transmission, airborne transmission through fine particle aerosol can rarely occur. Therefore, airborne precautions using a negative air pressure room with high efficiency particulate air filtration should be initiated immediately for hospitalized high risk or confirmed smallpox patients. This is the same isolation precaution that is taken for other infectious diseases with respiratory transmission, such as varicella.

All personnel who have contact with a suspected or confirmed case of smallpox should utilize appropriate protective equipment. This includes using properly fitted respirators (masks) of N95 quality or higher. In addition, personnel should use disposable gloves, gowns and shoe covers for all contact with patients. This precaution is to prevent inadvertent transmission of variola virus from clothing or other contaminated items to susceptible persons. Personnel should remove and correctly dispose of all protective clothing before contact with other people. Reuseable bedding and clothing can be autoclaved or laundered in hot water with bleach to inactivate the virus. People who come into contact with materials potentially contaminated with smallpox virus, such as laundry handlers, housekeeping, and laboratory personnel should utilize appropriate protective equipment. If a case of smallpox is confirmed, these personnel should be vaccinated before handling contaminated materials.

Medical management of a person with smallpox is primarily supportive. No antiviral drug is currently approved by the Food and Drug Administration for the treatment of smallpox. Recent studies suggest that the antiviral drug cidofovir might be useful as a therapeutic agent. However, the drug must be administered intravenously, and can cause serious renal toxicity. Cidofovir administered for the treatment of smallpox would be an off-label use. Antiviral therapy with cidofovir or other drugs subsequently found to have anti- variola activity might be considered but would be used under an investigational new drug protocol and by an infectious diseases specialist.

Smallpox Epidemiology

- Reservoir            Human (before eradication)
- Transmission       Respiratory by large particles  
Can be airborne
- Communicability    From onset of rash until  
all crusts separate

EPIDEMIOLOGY

RESERVOIR

Although animals can be experimentally infected with variola, humans are the only natural host. There is no chronic carrier state, and no known animal reservoir. Since the early 1980s (*i.e.*, following global smallpox eradication) the only known locations of variola virus are at the CDC in Atlanta, and at the State Research Center of Virology and Biotechnology in Koltsovo, Russia.

## TRANSMISSION

Transmission of smallpox occurs through inhalation of airborne variola virus, usually droplets expressed from the oral, nasal, or pharyngeal mucosa of an infected person. Most transmission results from direct face-to-face contact with an infected person, usually within a distance of 6 feet, or from physical contact with a person with smallpox or contaminated articles. Although variola virus could remain viable for years in dried crusts of skin lesions, transmission from crusts is uncommon, probably because virus is enmeshed in a fibrin matrix.

## COMMUNICABILITY

A person infected with variola virus is not infectious during the incubation period, or the first day or two of the prodromal stage of the illness. The patient becomes infectious with the first appearance of the rash, which was often accompanied by lesions in the mouth and pharynx. The patient becomes infectious and can transmit the virus throughout the course of the illness (*i.e.*, until all crusts separated). Transmission is most frequent during the first week of the rash, while most skin lesions are intact (*i.e.*, vesicular or pustular). Virus is present in material draining from ruptured pustules and in crusts for a longer period, but infection from this source appears to be less frequent. In general persons with a severe rash and involvement of the mouth and pharynx, and those with a cough are more infectious than those with a slight rash. Household secondary attack rates are generally 50%-60%.

Natural transmission of smallpox in a population is relatively slow. There is an interval of two to three weeks between each generation of cases. Smallpox generally spreads less widely and less rapidly than varicella or measles, probably because transmission of variola virus doesn't occur until the onset of rash and generally requires close face to face contact for spread. At the time of rash onset, most patients are already confined to bed because of the high fever and toxemia of the prodromal stage of the illness. However, people with severe prodromal illness may seek medical attention. Consequently, hospitals are a frequent source of infection because of transmission from unrecognized hospitalized cases.

Secondary cases of smallpox are usually limited to those who come in contact with the infected person in the household or hospital. During the global eradication program, it was possible to interrupt the chain of transmission of smallpox by isolating smallpox patients in a setting in which they had contact only with adequately vaccinated or previously infected people. This limited the next potential generation of cases to the household and close contacts of the index case or cases. Contacts were identified and immediately vaccinated. Contacts who became ill were also isolated to establish a barrier to further transmission. This strategy was found to be effective even if community vaccination levels were low.

### Smallpox Epidemiology

- Most transmission results from face-to-face contact with infected person (household and hospital contacts)
- Transmission most frequent during first week of rash

## Smallpox Eradication

- Intensified Global Eradication program begun in 1967
- Initial strategy was mass vaccination
- Strategy evolved to “surveillance and containment”
- Last indigenous case in Somalia in October 1977

## TEMPORAL PATTERN

In temperate areas, the seasonality of smallpox was similar to that of measles and varicella, with incidence highest during the winter and spring. In tropical areas, seasonal variation was decreased and the disease was present throughout the year.

## SECULAR TRENDS

The last case of smallpox in the United States was reported in 1949. In the early 1950s, an estimated 50 million cases of smallpox occurring worldwide each year. Ten to 15 million cases occurred in 1967, when the disease had already been eliminated in 80 percent of the world.

## SMALLPOX ERADICATION

The intensified global smallpox eradication program began in 1967. The initial campaign was based on a two-fold strategy. First, mass vaccination campaigns in each country, using vaccine of ensured potency and stability, that would reach at least 80% of the population. Second, the development of surveillance systems to detect and contain cases and outbreaks.

The program had to surmount numerous problems, including lack of organization in national health services, epidemic smallpox among refugees fleeing areas stricken by civil war and famine, shortages of funds and vaccine, and a host of other problems posed by difficult terrain, climate, and cultural beliefs. In addition, it was soon learned that even when 80% of the population was vaccinated, smallpox often persisted.

Soon after the program began it became apparent that by isolating people with smallpox and vaccinating their contacts, outbreaks could be more rapidly contained, even in areas where vaccination coverage was low. This strategy was called **surveillance and containment**, and it became the key element in the global eradication program.

Although setbacks occurred, the surveillance and containment strategy was an enormous success. Using it, the last case of smallpox in Brazil was reported in 1971, and Indonesia's last case occurred in 1972. India, Pakistan and Bangladesh, with a population at that time of more than 700 million, was a particular challenge. But with intensive house to house searches and strict containment, the last case of variola major- the most deadly type of smallpox- occurred in Bangladesh in October 1975.

By the end of 1975, smallpox persisted only in the Horn of Africa. Conditions were very difficult in Ethiopia and Somalia, where there were few roads. Civil war, famine, and refugees made the task even more difficult. An intensive surveillance and containment and vaccination program was undertaken in the spring and summer of 1977. As a result, the world's last indigenous patient

with smallpox was a hospital cook in Merka, Somalia, on October 26, 1977. Searches for additional cases continued in Africa for more than 2 years, during which time thousands of rash illnesses were investigated. None proved to be smallpox.

The last cases of smallpox on earth occurred in an outbreak of 2 cases (one of which was fatal) in Birmingham, England in 1978. This outbreak is believed to have occurred because variola virus was carried by the ventilation system from a research laboratory to an office one floor above the laboratory. The World Health Organization officially certified that smallpox had been eradicated on December 9, 1979, two years after the last case in Somalia. In 1980 the World Health Assembly recommended that all countries cease vaccination. The World Health Organization also recommended that all laboratories either destroy their remaining stocks of variola virus or transfer them to one of two WHO reference laboratories. All laboratories were believed to have complied with this request.

### CASE DEFINITION

A clinical case of smallpox is defined as an illness with acute onset of fever  $\geq 101^{\circ}$  F followed by a rash characterized by firm, deep-seated vesicles or pustules in the same stage of development without other apparent cause.

This case definition will not detect an atypical presentation of smallpox including hemorrhagic or flat-type disease. In addition, given the extremely low likelihood of smallpox occurring, a case definition has been developed that provides a high level of specificity (*i.e.*, vesicular rash illness), rather than a high level of sensitivity (*i.e.*, maculo-papular rash illness). In the event of a smallpox outbreak, the case definition would be modified to increase sensitivity.

### SMALLPOX (VACCINIA) VACCINE

Humans have attempted to prevent smallpox for more than 1,000 years. The first attempts were developed in China and India in the 9th century, and involved either nasal insufflation of powdered smallpox scabs, or scratching material from a smallpox lesion into the skin. This procedure was known as variolation, and if successful, produced lasting immunity to smallpox. However, because the person was infected with variola virus, a severe infection could result, and the person could transmit smallpox to others.

In 1796 **Edward Jenner**, a doctor in rural England, discovered that immunity to smallpox could be produced by inoculating a person with material from a cowpox lesion. Cowpox is poxvirus in the same family as variola. Jenner called the material used for inoculation vaccine, from the root word *vacca*, which is Latin for cow. The procedure was much safer than variolation, and did not involve a risk of smallpox transmission. Vaccination to prevent smallpox was soon practiced all over the world.

## Smallpox Vaccine

- Live vaccinia virus in calf lymph
- Diluent contains glycerin and trace amounts of polymyxin B, streptomycin, tetracycline, neomycin and phenol
- New vaccine produced using cell culture technology

## Response to Smallpox Vaccination

- Neutralizing antibody develops
  - 10 days after primary vaccination
  - 7 days after revaccination
- >95% of primary vaccinees develop detectable neutralizing antibody
- Antibody persists >10 years

## Smallpox Vaccine Efficacy

- Clinical efficacy estimated in household contact studies
- 91%-97% reduction in cases among contacts with vaccination scar
- Studies did not consider time since vaccination or potency of vaccine

At some time during the 19th century, the cowpox virus used for smallpox vaccination was replaced by vaccinia virus. Vaccinia is in the same family as cowpox and variola, but is genetically distinct from both. The origin of vaccinia virus, and how it came to be in the vaccine is not known.

## CHARACTERISTICS

The smallpox vaccine currently available in the United States is a **live-virus preparations of infectious vaccinia virus**. Smallpox vaccine does not contain smallpox (variola) virus. The current was prepared in the early 1980s from calf lymph with a seed virus derived from the New York City Board of Health (NYCBOH) strain of vaccinia virus. The vaccine is provided as a lyophilized (freeze-dried) powder in a 100-dose vial. The diluent used to reconstitute the vaccine is 50% glycerin, and contains the antibiotics polymyxin B, streptomycin, tetracycline and neomycin, and a small amount of phenol as a preservative.

Approximately 15 million doses of vaccine are available now in the United States. Studies are underway at the National Institutes of Health to determine if the current vaccine can be diluted further to provide additional doses. More than 200 million additional doses of vaccine are being produced to be available in case of an introduction of smallpox. The new vaccine is being produced by cell culture methods used to produce other vaccines commonly used in the United States.

The vaccine is administered by using a multiple-puncture technique with a special bifurcated needle, which first became available in 1965. In 1983 the smallpox vaccine was removed from the civilian market. The vaccine is currently available only from the Centers for Disease Control and Prevention under an Investigational New Drug (IND) protocol.

## IMMUNOGENICITY AND VACCINE EFFICACY

Neutralizing antibodies induced by vaccinia vaccine are genus-specific and cross-protective for other Orthopoxviruses (*e.g.*, monkeypox, cowpox, and variola viruses). Neutralizing antibodies are detectable 10 days after primary vaccination, and 7 days after revaccination. Although the level of antibody that protects against smallpox infection is unknown, after percutaneous administration of a standard dose of vaccinia vaccine, >95% of primary vaccinees (*i.e.*, persons receiving their first dose of vaccine) will develop neutralizing or hemagglutination inhibition antibody at a titer of >1:10. Neutralizing antibody titers of >1:10 persist among 75% of persons for 10 years after receiving second doses and up to 30 years after receiving three doses of vaccine.

The efficacy of smallpox vaccine has never been measured precisely in controlled trials. However, protection has been determined in studies of people exposed to a smallpox patient in their household.

These studies indicated a 91%-97% reduction in smallpox among contacts with a vaccination scar compared to contacts without a scar. However, these studies did not always consider the time since vaccination or potency of vaccine, so may underestimate protection.

Epidemiologic studies demonstrated that a high level of protection (nearly 100%) against smallpox persists for up to 5 years after primary vaccination and substantial but waning immunity for ten years or more. Antibody levels after revaccination can remain high longer, conferring a greater period of immunity than occurs after primary vaccination alone. Although smallpox vaccination in the remote past may not completely protect against smallpox, vaccinated people appear to have less severe disease. Studies of smallpox cases imported into Europe in the 1950s and 1960s demonstrated fewer fatalities among vaccinated people compared to those who were unvaccinated. The fatality rate among people vaccinated <10 years before exposure was 1.3%, 7% among those vaccinated 11 to 20 years prior, and 11% among those vaccinated 20 or more years prior to infection. In contrast, 52% of unvaccinated people died.

Smallpox vaccination also provides protection if administered after an exposure to smallpox. **Post-exposure efficacy** has been estimated in household contact studies in Pakistan and India. These studies indicate that secondary cases in households were reduced up to 91% compared to unvaccinated people. The lowest secondary attack rates occurred in persons vaccinated <7 days after exposure. In these studies, smallpox was generally less severe (*i.e.*, modified type) in persons who received post-exposure vaccination.

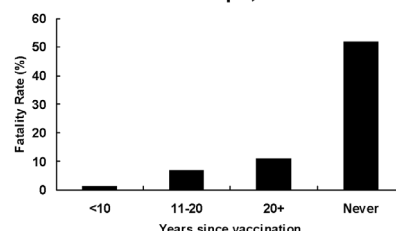
Following vaccination, vaccinia virus replicates in the basal cells of the epidermis, resulting in the development of a lesion at the site of vaccination. A papule develops at the inoculation site 3-5 days after primary vaccination. Approximately 7 days following primary vaccination, a vesicle surrounded by erythema (a "Jennerian vesicle") forms at the site. The vesicle becomes pustular by 7 to 11 days after vaccination. Maximum erythema occurs 8 to 12 after vaccination. The erythema then subsides, the pustule dries, and a crust develops 2 to 3 weeks after vaccination. By the end of the third week, the crust separates, leaving a permanent scar at the vaccination site. This response to vaccination is called a **major reaction**, and indicates that virus replication has taken place and vaccination was successful. **A person is considered protected with the development of a major reaction at the vaccination site.** A revaccinated person often develops a skin reaction similar to that after primary vaccination, but the lesion progresses faster than after primary vaccination.

Some persons do not develop a typical skin lesion after vaccination. All responses other than major reactions are referred to as **equivocal**. There are several possible causes of equivocal reactions. The person may be sufficiently immune to suppress viral replication. The person may be allergic to a component of the vaccine which leads to a hypersensitivity reaction at the site. An

#### Duration of Immunity Following Smallpox Vaccination

- High level of protection (~100%) for up to 5 years following vaccination
- Substantial but waning immunity for  $\geq 10$  years
- Reduction in disease severity among previously vaccinated persons

#### Smallpox Fatality Rate by Time Since Vaccination - Europe, 1950-1971\*



\*Mack TM. J Infect Dis 1972;125:161-9.

#### Post-Exposure Vaccine Efficacy

- Secondary attack rates reduced up to 91% compared to unvaccinated contacts
- Lowest disease rates among persons vaccinated <7 days after exposure
- Disease generally less severe (modified type) in persons receiving post-exposure vaccination

#### Clinical Response to Smallpox Vaccination\*

Symptom/sign	Time after Vac
Papule	3 days
Vesicle	5-6 days
Pustule	7-11 days
Maximum erythema	8-12 days
Scab	14 days
Scab separation	21 days

\*typical response in a nonimmune person

#### Clinical Response to Smallpox Vaccination

- Major (primary) reaction
  - Indicates viral replication has occurred and vaccination was successful
  - Considered to be protected with the development of a major reaction
- Equivocal reaction
  - Indicates immune suppression of viral replication, allergic reaction without production of immunity, incorrect vaccination technique, or impotent vaccine

## Evolution of Smallpox Vaccine Recommendations

- 1971 Discontinue routine vaccination
- 1976 Discontinue vaccination of HCWs
- 1980 Vaccine recommended for lab workers
- 1991 Consider vaccine for HCWs exposed to recombinant vaccinia
- 2001 Bioterrorism guidelines

## Smallpox Vaccine Indications in Nonemergency Situations

- Laboratory workers who handle cultures or animals infected with nonhighly attenuated vaccinia\*
- Laboratory workers exposed to other Orthopoxviruses that infect humans
- Consider for other health care workers with contact with contaminated material

\*e.g., NYCBOH, Temple of Heaven, Copenhagen, Lister vaccinia and nonhighly attenuated recombinants

## Smallpox Vaccine Indications in Emergency Situations\*

- Persons exposed to initial release
- Close contact with confirmed or suspected case
- Direct care or transportation of confirmed or suspected case
- Laboratory personnel
- Persons with risk of contact with infectious materials from case

\*following confirmation of a case of smallpox

## Smallpox Vaccine

- **Schedule**
  - 1 successful dose  $\geq 18$  years of age
- **Revaccination**
  - 10 years (nonhighly attenuated vaccinia and recombinants)
  - 3 years (more virulent Orthopoxviruses)

equivocal reaction could also be caused by insufficiently potent vaccine or incorrect administration technique. In general, a person who has an equivocal response to vaccination should be revaccinated using vaccine from another vial if possible. More information on interpretation of response to vaccination is available in the smallpox vaccine ACIP statement.

## VACCINATION SCHEDULE AND USE

Routine childhood smallpox vaccination was discontinued in the United States in 1971. Routine vaccination of health care workers was discontinued in 1976, and among military recruits in 1990. In 1980 smallpox vaccine was recommended for laboratory workers who were at occupational risk for exposure to vaccinia or other orthopoxviruses. In 1991 the Advisory Committee on Immunization Practices recommended that other health care workers who could be exposed to vaccinia or recombinant vaccinia be considered for vaccination. Guidelines for use of smallpox vaccine in the event of an intentional release of smallpox virus were first published in 2001.

**Vaccination is currently recommended only for laboratory workers who directly handle cultures or animals contaminated or infected with non-highly attenuated vaccinia viruses** (e.g., the NYCBOH, Temple of Heaven, Copenhagen, or Lister vaccinia strains), and recombinant vaccinia viruses derived from nonhighly attenuated vaccinia strains. Vaccination is also recommended for laboratory workers exposed to other orthopoxviruses that infect humans (e.g., monkeypox or cowpox). Vaccination can be considered for other health-care workers who come into contact with materials such as dressings that may be contaminated with vaccinia or recombinant vaccinia. This could occur, for example, in the course of a clinical trial in which humans were administered vaccines containing recombinant vaccinia viruses.

**In the event of an intentional release of variola virus, vaccination would be recommended for those exposed to the initial release, contacts of people with smallpox, and others at risk of exposure.** Persons at risk of exposure would include those involved in the direct medical or public health evaluation, care or transportation of confirmed or suspected smallpox patients; laboratory personnel who collect or process clinical specimens from confirmed or suspected smallpox patients; and people who may have contact with infectious materials, such as those responsible for medical waste disposal, linen disposal or disinfection, and room disinfection in a facility where smallpox patients are present.

The **schedule** for smallpox vaccine is 1 successful dose (*i.e.*, a dose that results in a major reaction at the vaccination site). Under routine circumstances the vaccine should not be administered to persons <18 years of age. In an emergency (post-release) situation, there would be no age limit for vaccination of persons exposed to a person with confirmed smallpox.

Persons with occupational exposure to nonhighly attenuated vaccinia viruses, recombinant viruses derived from nonhighly attenuated vaccinia viruses, or other nonvariola orthopoxviruses should be revaccinated at least every 10 years. To ensure an increased level of protection against more virulent nonvariola orthopoxviruses (*e.g.*, monkeypox), empiric revaccination every 3 years can be considered.

## ADVERSE REACTIONS FOLLOWING VACCINATION

Smallpox vaccine contains live vaccinia virus, which replicates at the site of vaccination. In addition to a lesion at the site of vaccination (described above), primary vaccination can produce swelling and tenderness of axillary and other regional lymph nodes, beginning 3-10 days after vaccination and persisting for 2-4 weeks after the skin lesion has healed. A fever is also common after the vaccine is administered. Approximately 70% of children experience  $\geq 1$  days of temperatures  $\geq 100^{\circ}\text{F}$  for 4-14 days after primary vaccination, and 15%-20% of children experience temperatures  $\geq 102^{\circ}\text{F}$ . Fever is less common among adults after vaccination or revaccination.

Vaccinia virus is present at the site of vaccination beginning about 3 days after vaccination. Maximum viral shedding from the vaccination site occurs 4-14 days after vaccination, but vaccinia can be recovered from the site until the crust separates from the skin.

**Inadvertent autoinoculation** (*i.e.*, transfer of vaccinia from the vaccination site to another part of the body) is the most frequent complication of smallpox vaccination and accounts for approximately half of all complications of primary vaccination and revaccination. Studies in 1968 estimated one case of inadvertent autoinoculation for approximately every 1,890 primary vaccination doses. The most common sites involved are the face, eyelid, nose, mouth, genitalia, and rectum. Most lesions heal without specific treatment.

A variety of **erythematous or urticarial rashes** can occur approximately 10 days after primary vaccination. The vaccinee is usually afebrile with this reaction, and the rash resolves spontaneously within 2-4 days. Rarely, bullous erythema multiforme (Stevens-Johnson syndrome) occurs.

Moderate and severe complications of vaccinia vaccination include eczema vaccinatum, generalized vaccinia, progressive vaccinia, and postvaccinal encephalitis. These complications are rare but occur  $>10$  times more often among primary vaccinees than among revaccinees and are more frequent among infants than among older children and adults. **Eczema vaccinatum** is a localized or systemic dissemination of vaccinia virus among persons who have eczema or a history of eczema or other chronic or exfoliative skin conditions (*e.g.*, atopic dermatitis), or among contacts of vaccinees with eczema or a history of eczema. Eczema vaccinatum can occur regardless of whether the skin disease is active or quiescent. Usually the illness is mild and self-limited but can be severe or

### Smallpox Vaccine Adverse Reactions

- Inadvertent autoinoculation
- Eczema vaccinatum
- Generalized vaccinia
- Progressive vaccinia (vaccinia necrosum)
- Postvaccinal encephalitis
- Other dermatologic conditions

Rates of Reported Adverse Reactions  
Following Smallpox Vaccination – U.S., 1968

Complication	Rate per Million doses	Rate
IA	529	1/1,890
GV	242	1/4,132
EV	39	1/25,641
PV	1.5	1/666,666
PE	12	1/83,333
Total	1254	1/797

Lane JM, et al. J Infect Dis 1970;122:303-9.

### Inadvertent Autoinoculation

- Caused by transfer of vaccinia virus from site of vaccination to other areas of the body
- Most commonly on face, eyelid, nose, mouth, rectum, genitalia
- Most lesions heal spontaneously without specific treatment

### Eczema Vaccinatum

- Generalized spread of vaccinia on skin of patients with eczema or past history of eczema
- Occurs in vaccinees and contacts
- Can occur whether eczema is active or quiescent
- May be severe or fatal

## Generalized Vaccinia

- Results from viremia with implantations in the skin
- Occurs in the absence of eczema or other preexisting skin diseases
- Vesicles or pustules on normal skin distant from vaccination site
- Usually minor illness with little residual damage

## Progressive Vaccinia

- Progressive necrosis at site of vaccination, often with metastatic lesions
- Occurs in patients with impaired immunologic function, particularly cellular immunodeficiency
- Frequently fatal

## Postvaccinal Encephalitis

- Highest risk among children <12 months of age
- Believed to result from autoimmune or allergic reaction
- Frequently fatal or neurologic sequelae

## Fetal Vaccinia

- <50 fetal vaccinia cases reported in world literature
- Most result from primary vaccination of mother early in pregnancy
- Usually results in stillbirth or death of infant soon after delivery

fatal. The most serious cases among vaccine recipients occur among primary vaccinees. Severe cases have been observed after contact of recently vaccinated persons with persons who have active eczema or a history of eczema. Eczema vaccinatum is estimated to occur once per 25,000 primary vaccination doses.

**Generalized vaccinia** is another type of rash following smallpox vaccination. This condition is believed to result from a vaccinia viremia with implantations in the skin in persons without eczema or other preexisting skin disease. It consists of vesicles or pustules appearing on normal skin distant from the vaccination site. Most rashes labeled as generalized vaccinia produce only minor illness with little residual damage. The rash is generally self-limited and requires minor or no therapy except among patients whose conditions might be toxic or who have serious underlying immunosuppressive illnesses. Rashes diagnosed as generalized vaccinia occurs at a rate of about once per 4,000 primary vaccinations.

**Progressive vaccinia**, also known as vaccinia necrosum, is a severe illness characterized by progressive necrosis in the area of vaccination, often with metastatic lesions. It occurs almost exclusively among persons with cellular immunodeficiency, but can occur in persons with humoral immunodeficiency. It occurs approximately once per 600,000 primary vaccinations, and was almost always fatal before the introduction of vaccinia immune globulin and antiviral agents. Progressive vaccinia may be more common now, with HIV and post transplant immunosuppression widely prevalent.

**Postvaccinal encephalitis** occurs once in about 80,000 primary vaccinations. In the majority of cases, postvaccinal encephalitis affects primary vaccinees <12 months of age or adolescents and adults receiving a primary vaccination. It presents with any of a variety of central nervous system signs, such as ataxia, confusion, paralysis, seizures, or coma. Most cases are believed to result from autoimmune or allergic reactions rather than direct viral invasion of the nervous system. Approximately 15%-25% percent of affected vaccinees with this complication die, and 25% develop permanent neurological sequelae.

**Fetal vaccinia** is a rare complication of smallpox vaccination. Fewer than 50 cases of fetal vaccinia infection have been reported, usually after primary vaccination of the mother in early pregnancy. Fetal vaccinia usually results in stillbirth or death of the infant soon after delivery. Smallpox vaccine is not known to cause congenital malformations.

**Death** resulting from smallpox vaccination is rare, with approximately 1 death per million primary vaccinations and 1 death per 4 million revaccinations. Death is most often the result of postvaccinal encephalitis or progressive vaccinia.

## CONTRAINDICATIONS AND PRECAUTIONS TO VACCINATION

As with all vaccines, smallpox vaccine is contraindicated for persons who have experienced a **serious allergic reaction to a prior dose of vaccine, or to a vaccine component**.

Reconstituted vaccine contains trace amounts of polymyxin B, streptomycin, tetracycline, neomycin, and phenol. The vaccine does not contain penicillin.

People with significant **immunosuppression**, or who have an **immunosuppressed household contact** should not routinely receive smallpox vaccine. Replication of vaccinia virus can be enhanced among people with immunodeficiency diseases and immunosuppression. Significant immunosuppression can be caused by many diseases, including leukemia, lymphoma, generalized malignancy; solid organ or stem cell transplantation; and cellular or humoral immunity disorders, including HIV infection. Drugs that can cause immunosuppression include alkylating agents, antimetabolites, radiation, or high dose corticosteroid therapy. Many experts suggest that prednisone doses of 2 milligrams per kilogram of body weight per day or higher or 20 milligrams per day or higher for 14 days or more be considered immunosuppressive for the purpose of live virus vaccination.

Live viral vaccines are contraindicated during **pregnancy**. Smallpox vaccine should not be administered to pregnant women for routine nonemergency indications.

Because of the increased risk for eczema vaccinatum, smallpox vaccine should not be administered to people with **eczema, a past history of eczema, those whose household contacts have active eczema, or a history of eczema**. People with other acute, chronic, or exfoliative skin conditions, such as atopic dermatitis, burns, or varicella zoster might also be at higher risk for eczema vaccinatum. These individuals should not be vaccinated until the condition resolves.

**Age <18 years** is a contraindication to vaccination in nonemergency circumstances. Since smallpox vaccine is only routinely indicated for people with occupational risk of exposure to vaccinia or recombinant vaccinia viruses, vaccination is not indicated for infants or children <18 years of age. As with all vaccines, vaccination should be deferred for people with **moderate or severe acute illnesses**.

In the event of an exposure to smallpox, there would be no contraindications to vaccination. In this situation, the benefit of vaccination would outweigh the risk of a complication from the vaccine. In a post-release situation, contraindications and precautions for use of smallpox vaccine in a person who has not been exposed to smallpox would be the same as those in a nonemergency situation.

### Smallpox Vaccine Contraindications and Precautions Nonemergency Situations

- Severe allergic reaction to prior dose or vaccine component
- Immunosuppression or immunosuppressed household contact
- Pregnancy
- Eczema, history of eczema, or household contact with eczema or history of eczema
- Other skin conditions
- Age <18 years

### Smallpox Vaccine Contraindications and Precautions Emergency (postrelease) Situations

- Exposed persons – no contraindications
- Unexposed persons – same as nonemergency situations

**Vaccinia Immune Globulin**

- Immunoglobulin fraction of plasma from persons vaccinated with vaccinia vaccine
- Effective for treatment of eczema vaccinatum, progressive vaccinia, severe generalized vaccinia, and ocular vaccinia
- Not effective in postvaccinal encephalitis
- Contraindicated in vaccinia keratitis

**VACCINIA IMMUNE GLOBULIN (VIG)**

The only product currently available for treatment of complications of vaccinia vaccination is VIG, which is an isotonic sterile solution of the immunoglobulin fraction of plasma from persons vaccinated with vaccinia vaccine. It is effective for treatment of eczema vaccinatum and certain cases of progressive vaccinia. It might be useful also in the treatment of ocular vaccinia resulting from inadvertent autoinoculation. However, VIG is contraindicated for the treatment of vaccinia keratitis. VIG is recommended for severe generalized vaccinia if the patient is extremely ill or has a serious underlying disease. VIG provides no benefit in the treatment of postvaccinal encephalitis and has no role in the treatment of smallpox. Current supplies of VIG are limited, and must be used under an Investigational New Drug (IND) protocol. VIG should be reserved for treatment of vaccine complications with serious clinical manifestations. The recommended dosage of the currently available VIG for treatment of complications is 0.6 ml/kg of body weight. VIG must be administered intramuscularly and should be administered as early as possible after the onset of symptoms. CDC is currently the only source of VIG for civilians.

**OTHER TREATMENT OPTIONS FOR SMALLPOX VACCINE COMPLICATIONS**

The Food and Drug Administration has not approved the use of any antiviral compound for the treatment of vaccinia virus infections or other orthopoxvirus infections, including smallpox. Certain antiviral compounds, such as cidofovir, have been reported to be active against vaccinia virus or other orthopoxviruses in vitro and among test animals. However, the safety and effectiveness of these compounds for treating vaccination complications or other Orthopoxvirus infections among humans is unknown. Questions also remain regarding the effective dose and the timing and length of administration of these antiviral compounds. Insufficient information exists on which to base recommendations for any antiviral compound to treat postvaccination complications or Orthopoxvirus infections, including smallpox.

**VACCINE STORAGE AND HANDLING**

Lyophilized smallpox vaccine is stable indefinitely at temperatures of  $-20^{\circ}\text{C}$  or less. Unreconstituted vaccine is stable for more than 1 year at room temperature. After reconstitution, smallpox vaccine is stable for 3 months at refrigerator temperature. Because the vaccine vial must be opened in order to prepare a dose for administration (*i.e.*, the bifurcated needle is dipped into the vaccine), care must be taken to avoid contamination. A needle should never contact the vaccine in a vial more than once.

**Vaccine Storage and Handling**

- Stable indefinitely at  $-20^{\circ}\text{C}$
- Unreconstituted vaccine stable for >1 year at room temperature
- Reconstituted vaccine stable for 3 months at refrigerator temperature
- Avoid contamination after opening vial

## SMALLPOX PREPAREDNESS AND RESPONSE PLANNING

A smallpox response plan has been in place in the United States since the early 1970s. In 1999, efforts were begun to update the response plan in the context of an intentional release of smallpox virus as an act of terrorism. Following the anthrax attacks in 2001 the plan was revised further to provide detailed information on surveillance and response to a smallpox virus release. An interim smallpox response plan was released in November 2001.

The interim plan is intended to assist with local and state response planning by identifying actions that must be taken in the event of a suspected smallpox case. **The key elements of preparedness for smallpox response are surveillance and diagnosis to achieve the early detection of an introduced case; isolation of the case or cases; and identification and vaccination of the contacts of the case or cases.**

A series of chapters, or guides, give detailed information on critical aspects of the plan. **Guide A contains surveillance, contact tracing, and epidemiologic investigations guidelines.** This includes pre-event rash surveillance, information on differential diagnosis, case definitions, and contact identification, tracing and surveillance, as well as data collection forms to support these activities.

**Guide B contains details on smallpox vaccine and vaccination,** including strategies, indications, contraindications, reconstitution, administration, and storage. It also describes recognition and surveillance of vaccine adverse events, guidelines for the use of vaccinia immune globulin, and contingencies for sterilization and reuse of needles. The current plan does not call for vaccination of the general public prior to the identification of a smallpox case. This is because smallpox vaccine has risks of adverse reactions. These risks are not acceptable in the absence of smallpox disease. The plan does describe the basic control strategy - isolation of patients with smallpox, identification and vaccination of contacts (and contacts of contacts), and monitoring contacts for development of illness. This strategy is called surveillance and containment, or ring vaccination, and was the fundamental approach of the global eradication program.

**Guide C describes isolation guidelines for both confirmed and suspected cases and febrile contacts of cases.** The issue of quarantine - that is, isolation of people before they become ill - is also discussed. **Guide D details specimen collection and transport.** **Guide E includes the communication plan and activities.** In the event of a smallpox outbreak, communications will be critical. This guide details strategies for communicating with the media, the public, and with providers. **Guide F describes decontamination guidelines,** including reusable medical equipment, medical waste, clothing, bedding, facilities and rooms, and vehicles used for transport of patient. Several annexes

### Smallpox Response Plan

- Interim plan released in November 2001
- Key elements:
  - Surveillance and investigation of cases
  - Contact tracing
  - Isolation guidelines
  - Specimen collection and handling
  - Communications
  - Decontamination

to the plan contain details of other issues likely to be encountered, including the general care of smallpox patients, vaccination clinic procedures, vaccine adverse event reporting. There are also a variety of forms and checklists to assist in preparing for and responding to a smallpox outbreak.

The current version of the Smallpox Response Plan and Guidelines, as well as additional information on bioterrorism and preparedness planning is available on the CDC Bioterrorism Preparedness website at <<http://www.bt.cdc.gov>>.

## SELECTED REFERENCES

CDC. Vaccinia (smallpox) vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2001;50(RR-10):1-25.

Fenner F, Henderson DA, Arita I, et al (eds). *Smallpox and its eradication*. Geneva: World Health Organization, 1988. Available from the World Health Organization website at <http://www.who.int/emc/diseases/smallpox/Smallpoxeradication.htm>

Henderson DA, Inglesby TV, Bartlett JG, et al. Smallpox as a biological weapon: medical and public health management. *J Am Med Assoc* 1999;281:2127-37.

Henderson DA, Moss B. Smallpox and vaccinia. In: Plotkin SA, Orenstein WA, eds. *Vaccines* (3rd edition). Philadelphia, PA: W.B. Saunders, 1999;74-97.

Lane JM, Ruben FL, Neff JM, Millar JD. Complications of smallpox vaccination, 1968: results of ten statewide surveys. *J Infect Dis* 1970;122:303-9.

LeDuc JW, Jahrling PB. Strengthening national preparedness for smallpox: an update. *Emerg Infect Dis* 2001;7. Available on the CDC website at <http://www.cdc.gov/ncidod/eid/vol7no1/leduc.htm>

Mack TM. Smallpox in Europe, 1950-1971. *J Infect Dis* 1972;125:161-9.

Rosenthal SR, Merchlinsky M, Kleppinger C, Goldenthal KL. Developing new smallpox vaccines. *Emerg Infect Dis* 2001;7. Available on the CDC website at <http://www.cdc.gov/ncidod/eid/vol7no6/rosenthal.htm>

WHO. Smallpox eradication: temporary retention of variola virus stocks. *Weekly Epidemiol Rec* 2001;19:142-45.